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Le et al.

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(54) **RECOMBINANT A2-SPECIFIC TNF α SPECIFIC ANTIBODIES**

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(52) **U.S. Cl.** **424/145.1; 424/130.1; 424/133.1; 424/141.1; 530/387.1; 530/387.3; 530/388.1; 530/388.23**

(58) **Field of Classification Search** **464/130.1, 464/145.1; 530/387.1, 388.23**

See application file for complete search history.

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(57) **ABSTRACT**

Anti-TNF antibodies, fragments and regions thereof which are specific for human tumor necrosis factor- α (TNF α) and are useful in vivo diagnosis and therapy of a number of TNF α -mediated pathologies and conditions, as well as polynucleotides coding for murine and chimeric antibodies, methods of producing the antibody, methods of use of the anti-TNF antibody, or fragment, region or derivative thereof, in immunoassays and immunotherapeutic approaches are provided.

22 Claims, 37 Drawing Sheets

EXHIBIT

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Page 2

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U.S. Patent

Jul. 4, 2006

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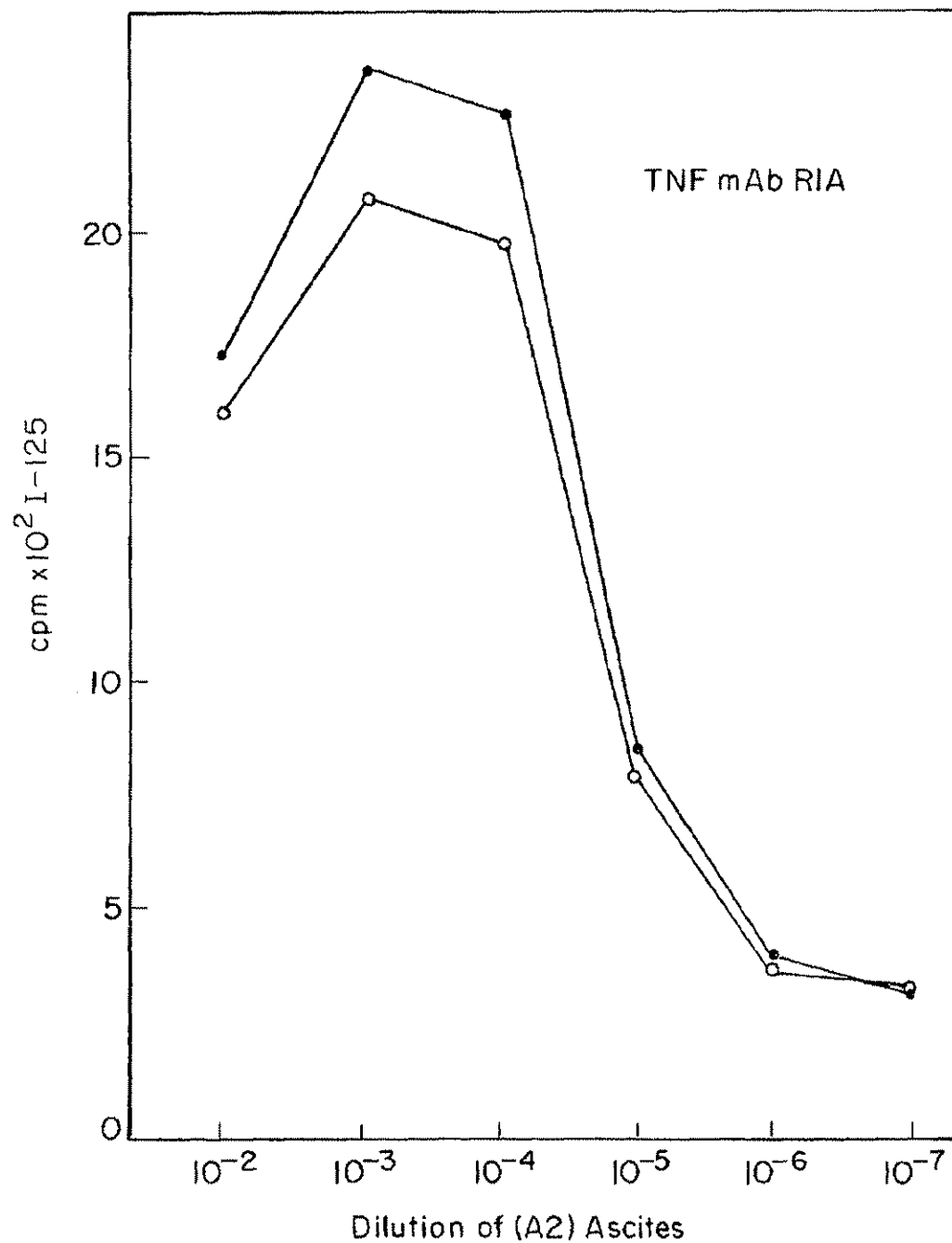


FIG. 1

U.S. Patent

Jul. 4, 2006

Sheet 2 of 37

US 7,070,775 B2

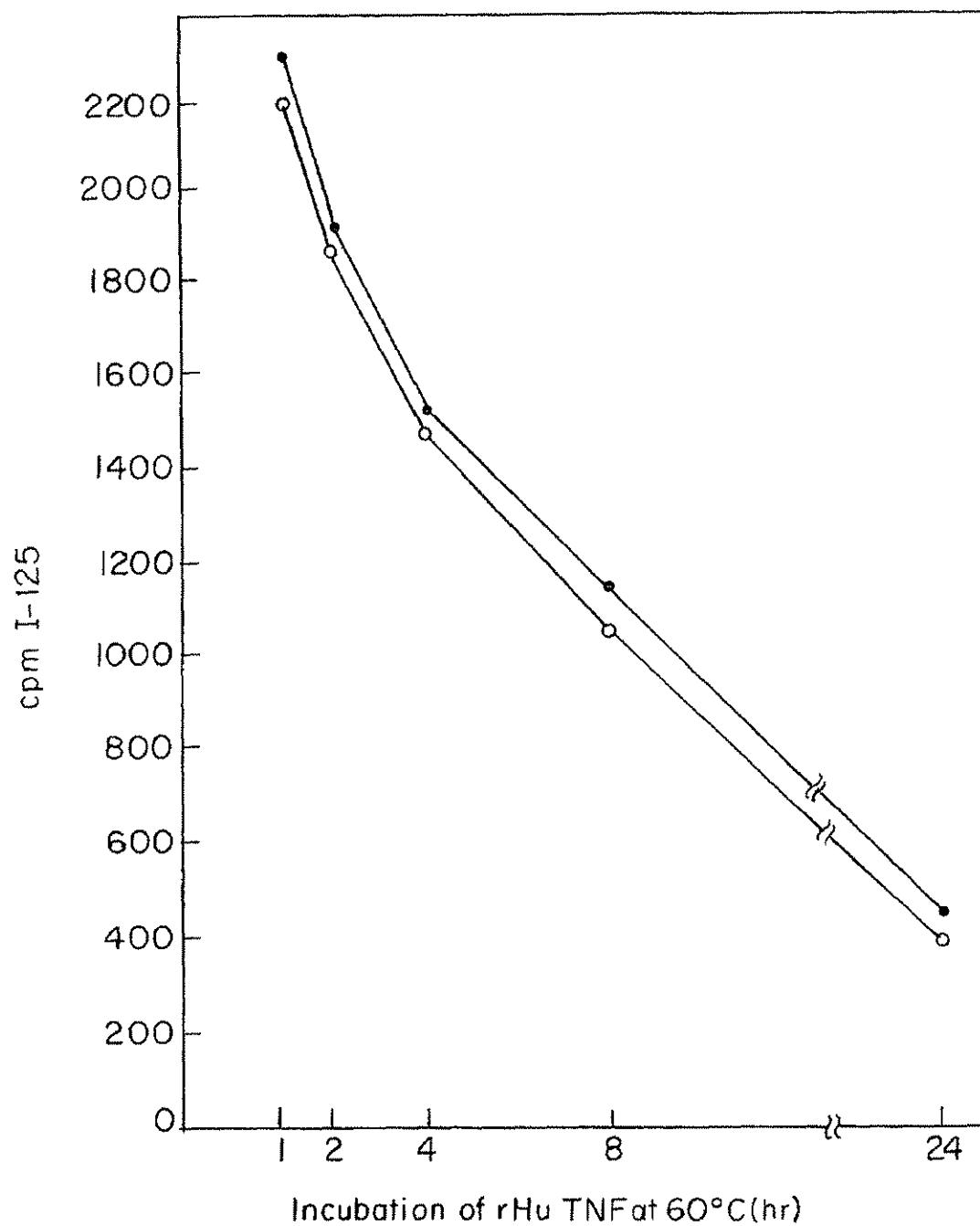


FIG. 2

U.S. Patent

Jul. 4, 2006

Sheet 3 of 37

US 7,070,775 B2

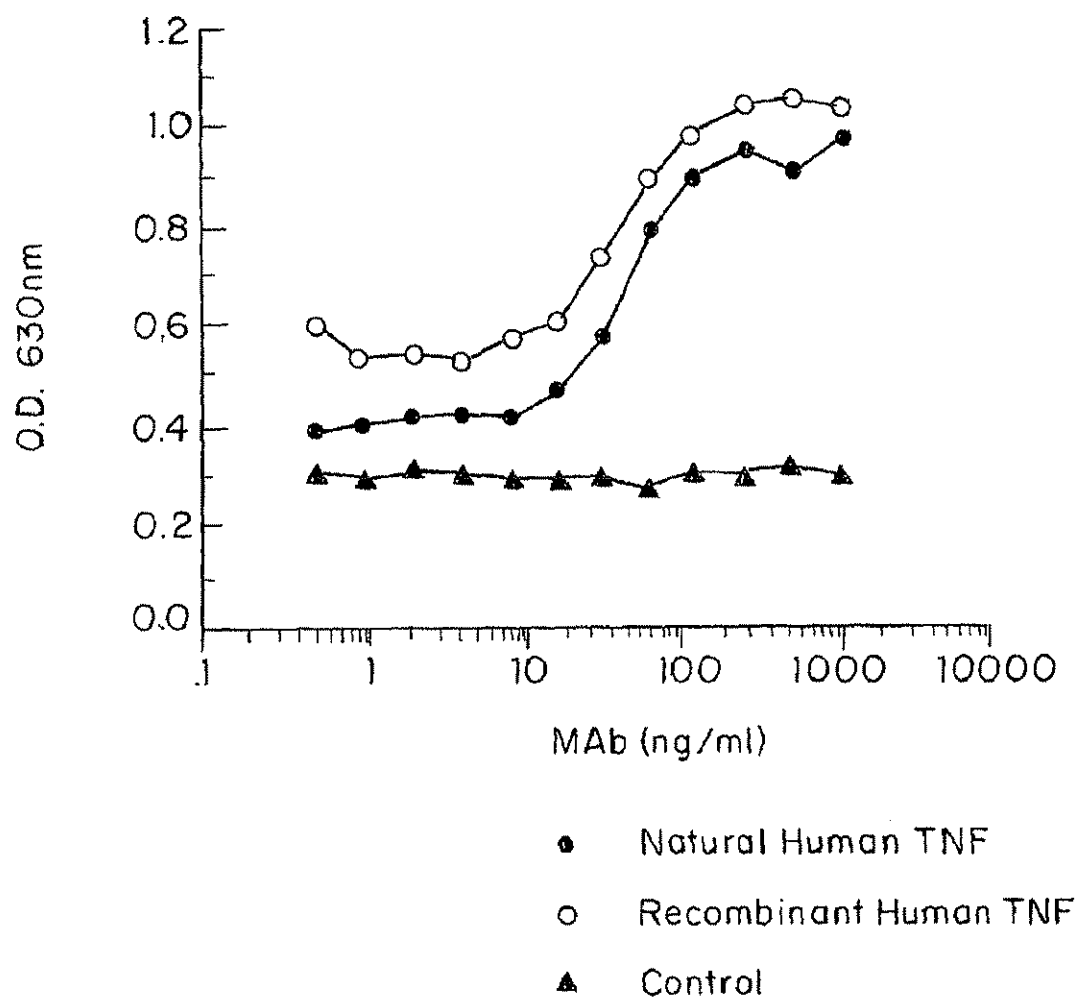


FIG. 3

U.S. Patent

Jul. 4, 2006

Sheet 4 of 37

US 7,070,775 B2

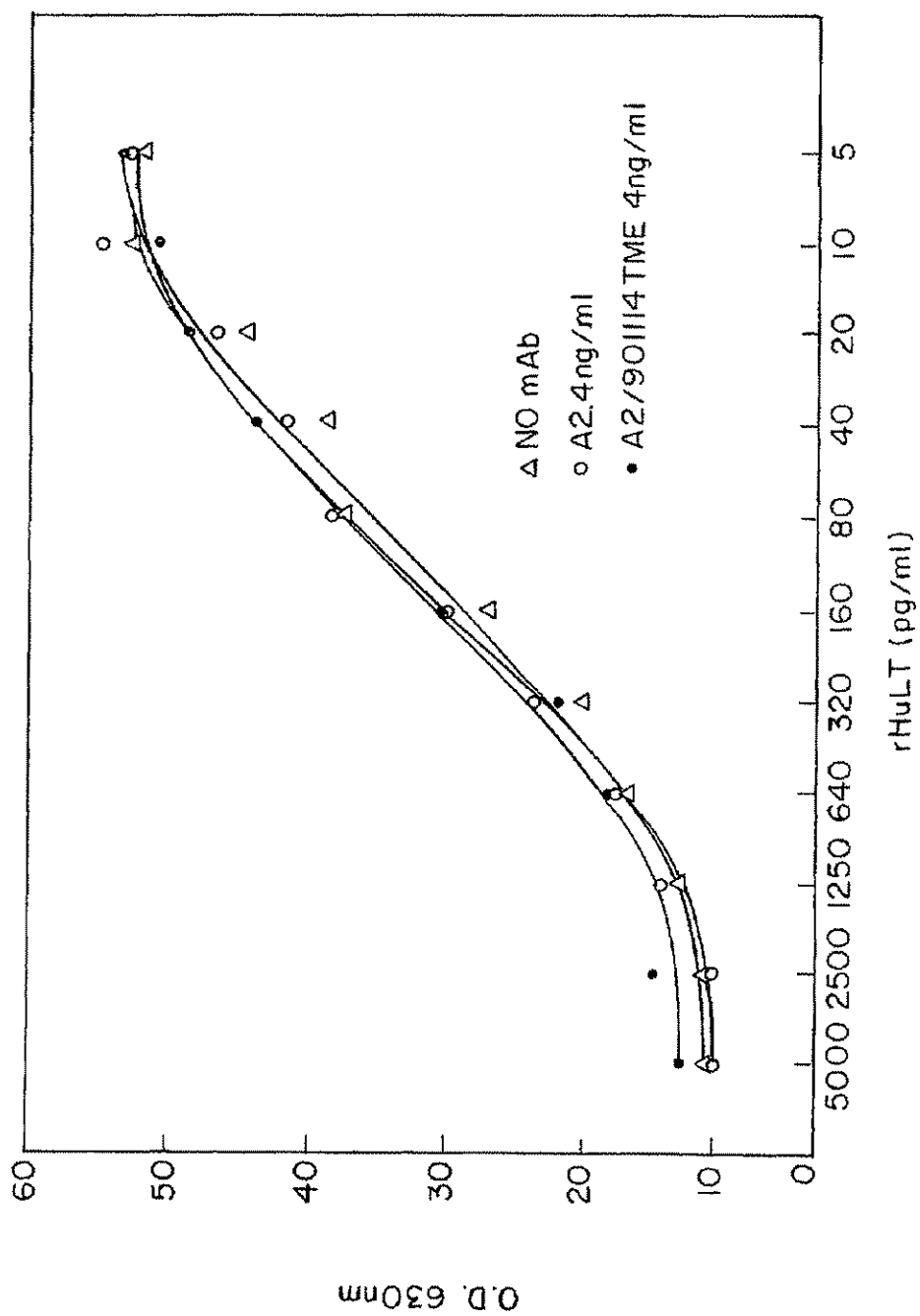


FIG. 4

U.S. Patent

Jul. 4, 2006

Sheet 5 of 37

US 7,070,775 B2

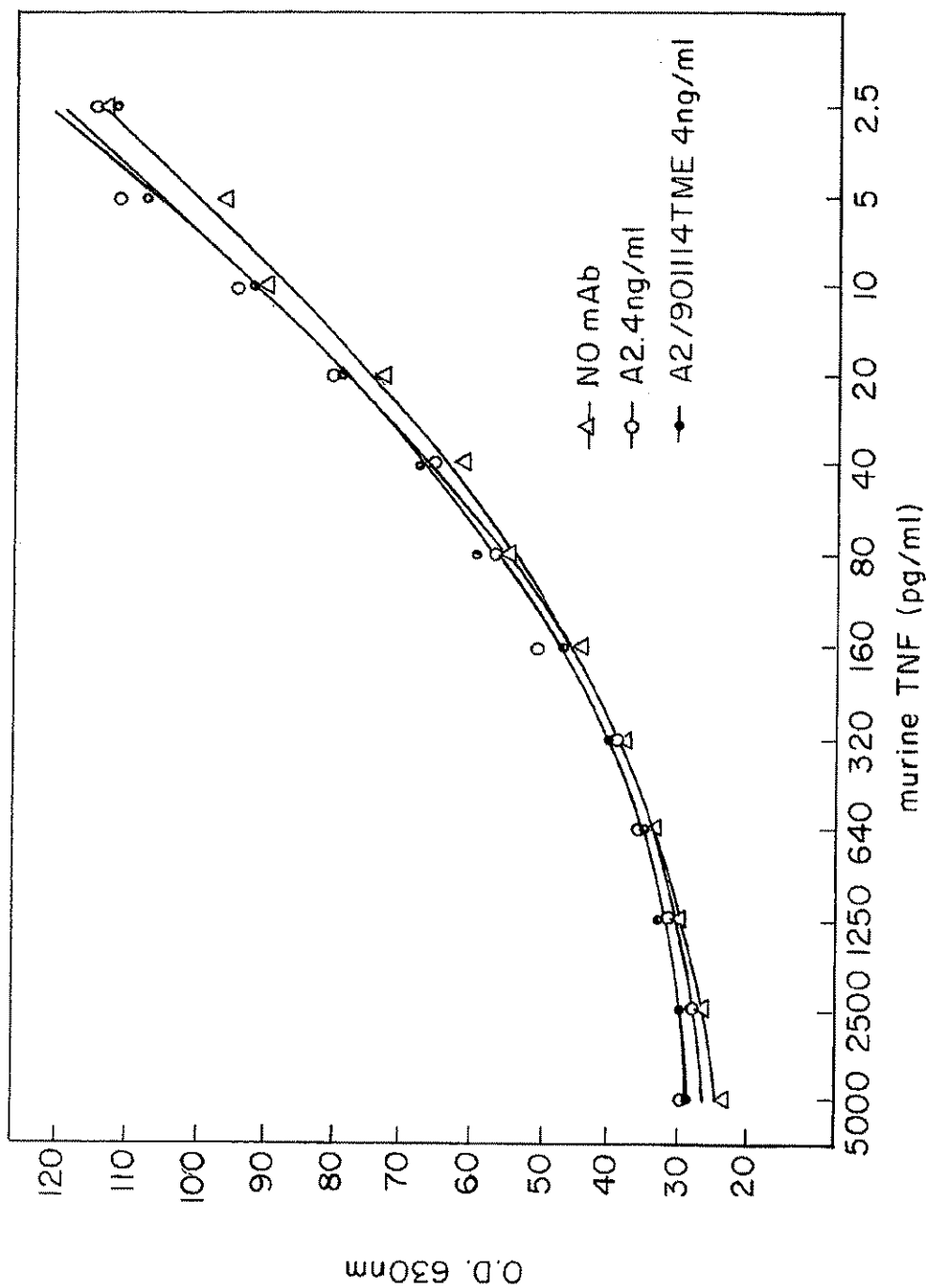


FIG. 5

U.S. Patent

Jul. 4, 2006

Sheet 6 of 37

US 7,070,775 B2

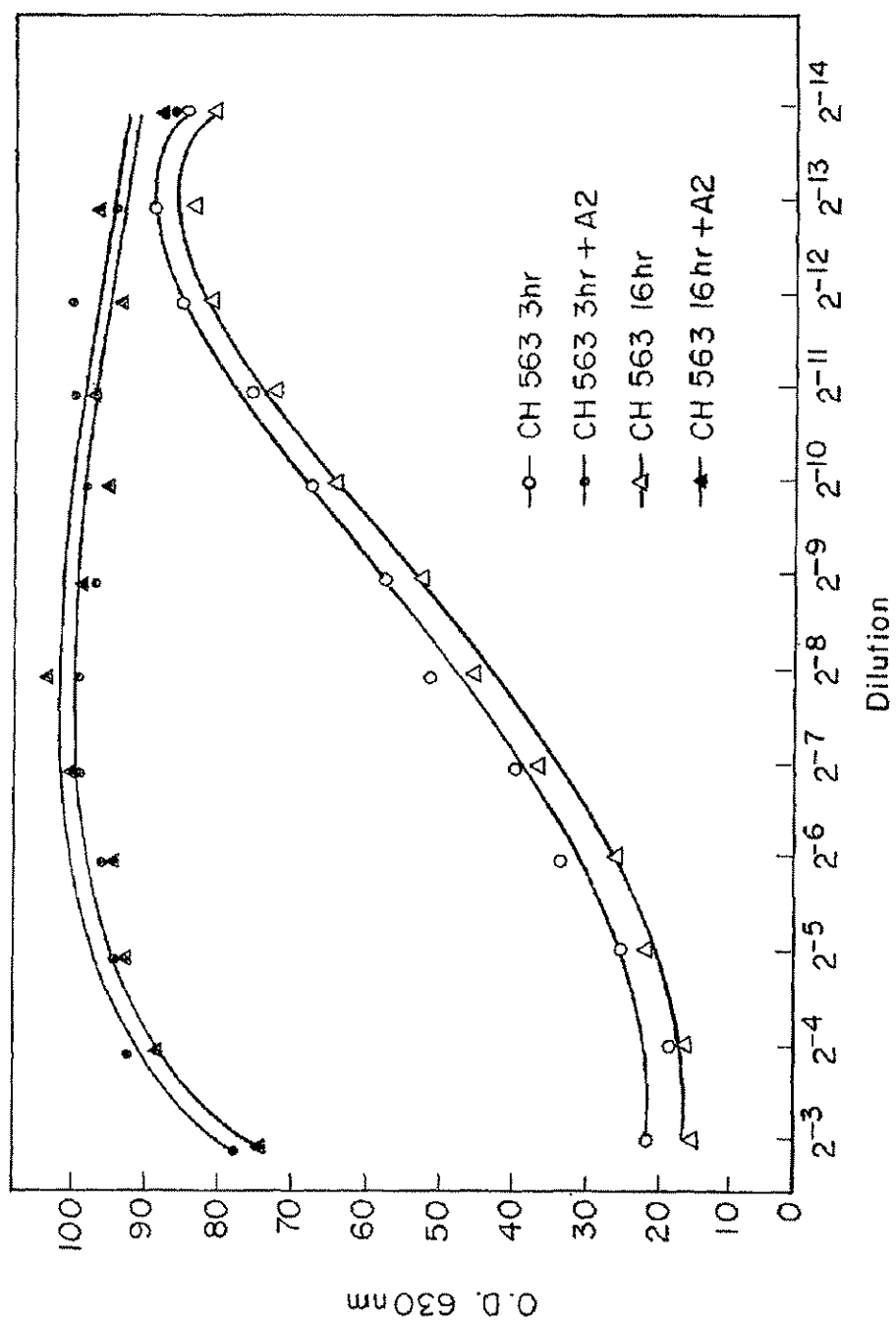


FIG. 6

U.S. Patent

Jul. 4, 2006

Sheet 7 of 37

US 7,070,775 B2

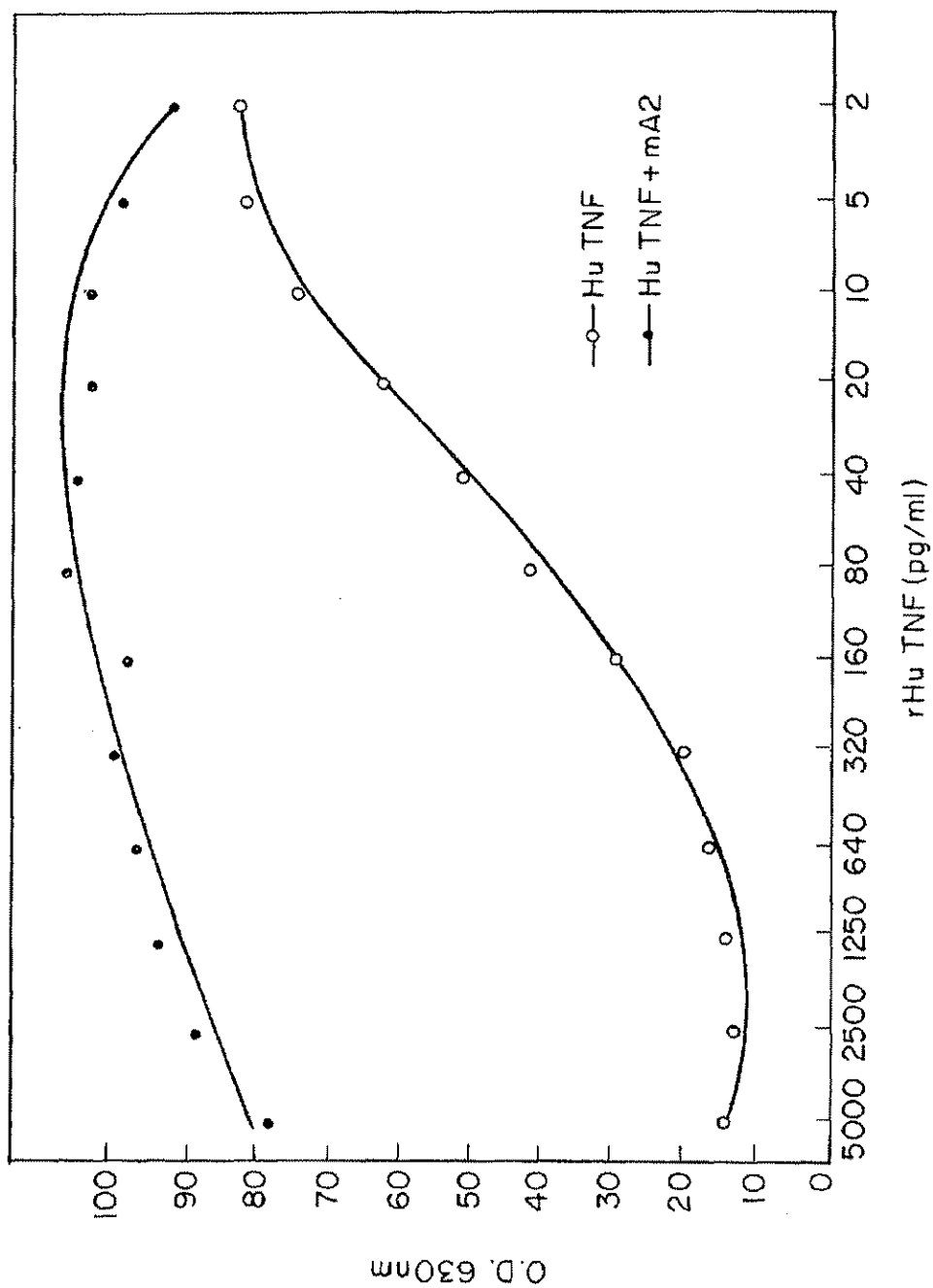


FIG. 7

U.S. Patent

Jul. 4, 2006

Sheet 8 of 37

US 7,070,775 B2

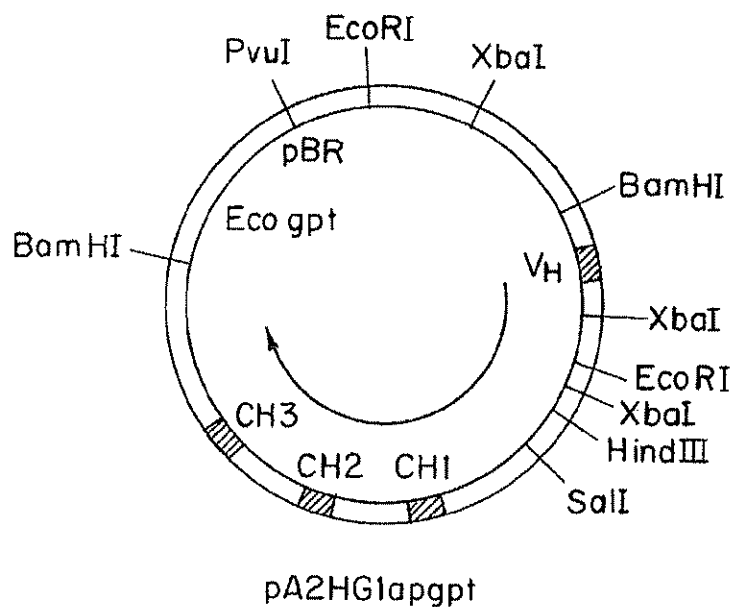


FIG. 8A

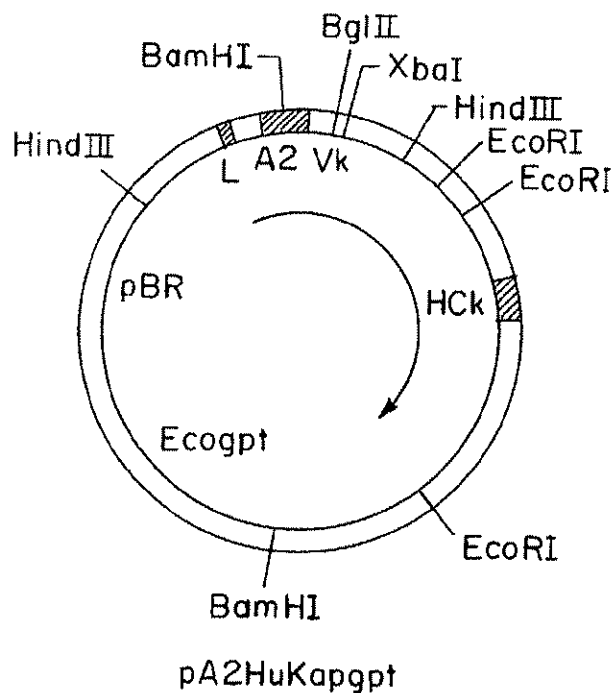


FIG. 8B

U.S. Patent

Jul. 4, 2006

Sheet 9 of 37

US 7,070,775 B2

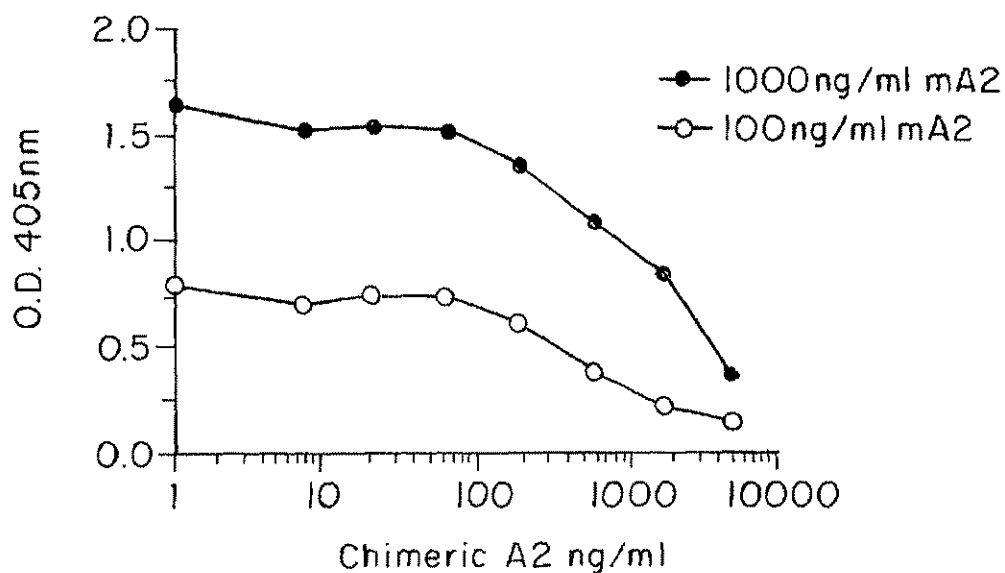


FIG. 9A

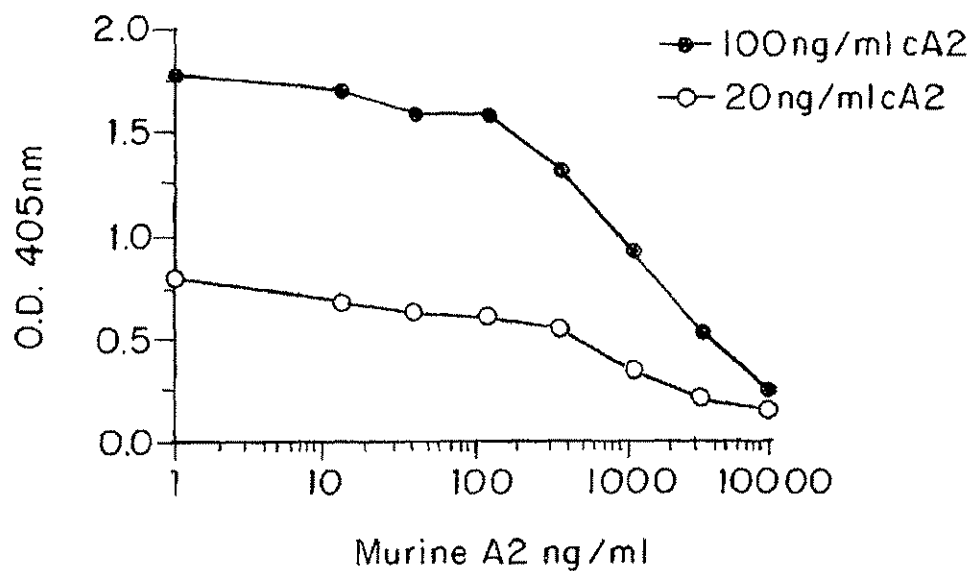


FIG. 9B

U.S. Patent

Jul. 4, 2006

Sheet 10 of 37

US 7,070,775 B2

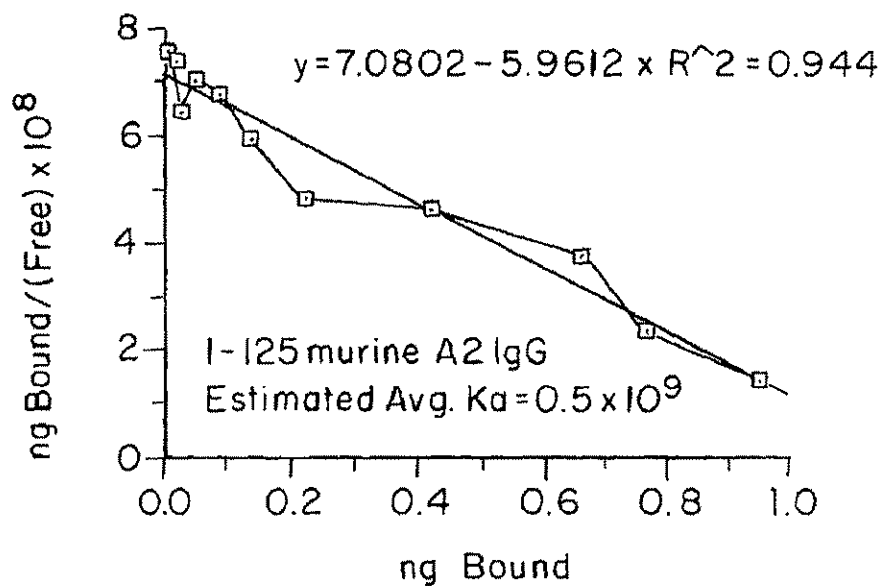


FIG. 10A

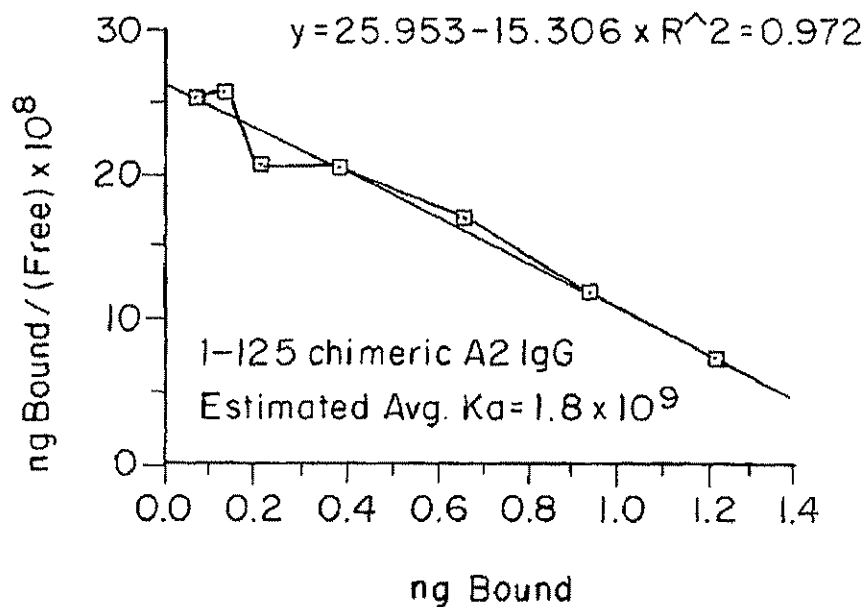


FIG. 10B

U.S. Patent

Jul. 4, 2006

Sheet 11 of 37

US 7,070,775 B2

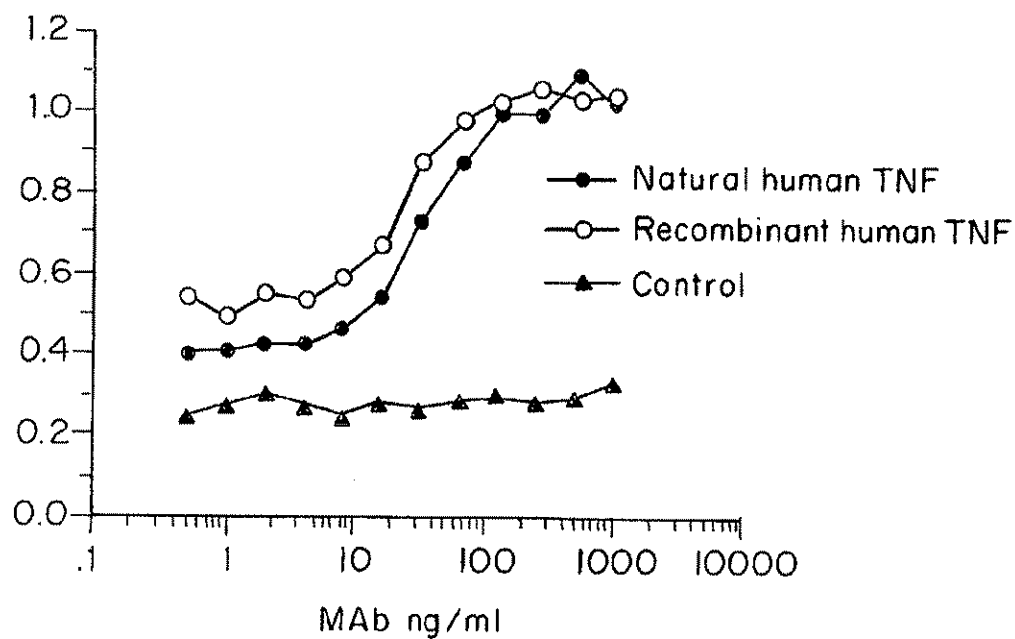


FIG. 11

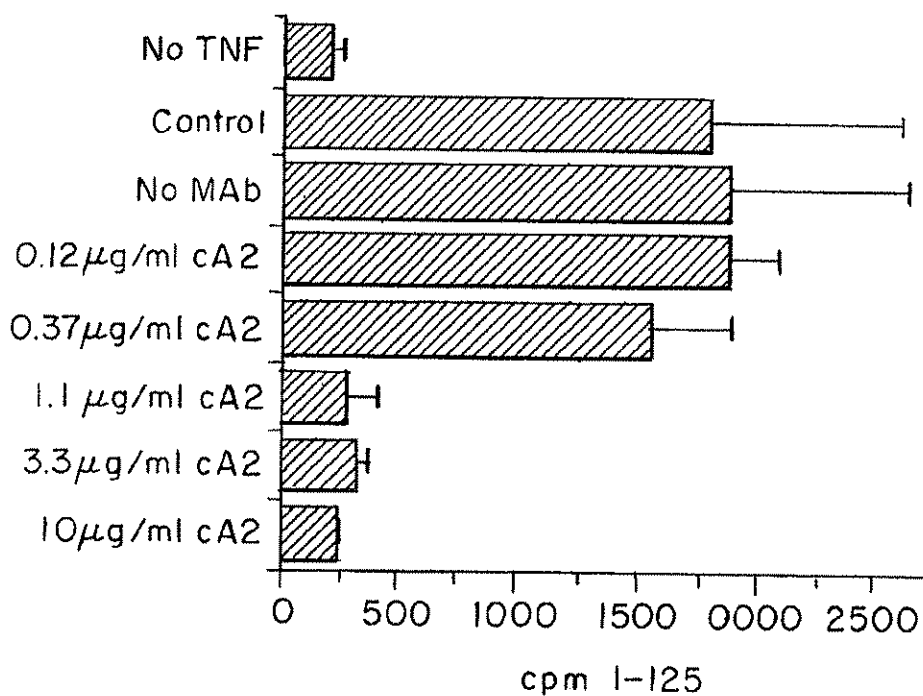


FIG. 12

U.S. Patent

Jul. 4, 2006

Sheet 12 of 37

US 7,070,775 B2

1 Val Arg Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro
 10
 21 Gln Ala Glu Gly Gln Leu Cln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala Asn Gly
 30
 41 Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser
 50
 61 Gln Val Leu Phe Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 70
 81 Ser Arg Ile Ala Val Ser Tyr Cln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro
 90
 101 Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile Tyr Leu
 110
 121 Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp
 130
 141 Tyr Leu Asp Phe Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
 150

FIG. 13

U.S. Patent

Jul. 4, 2006

Sheet 13 of 37

US 7,070,775 B2

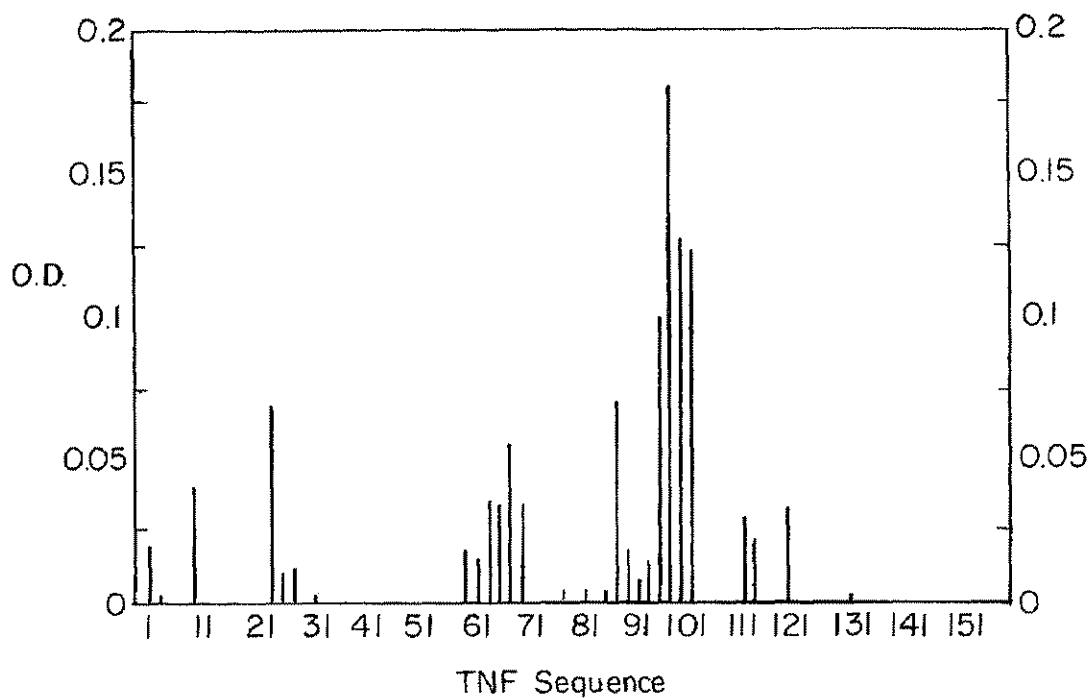


FIG. 14A

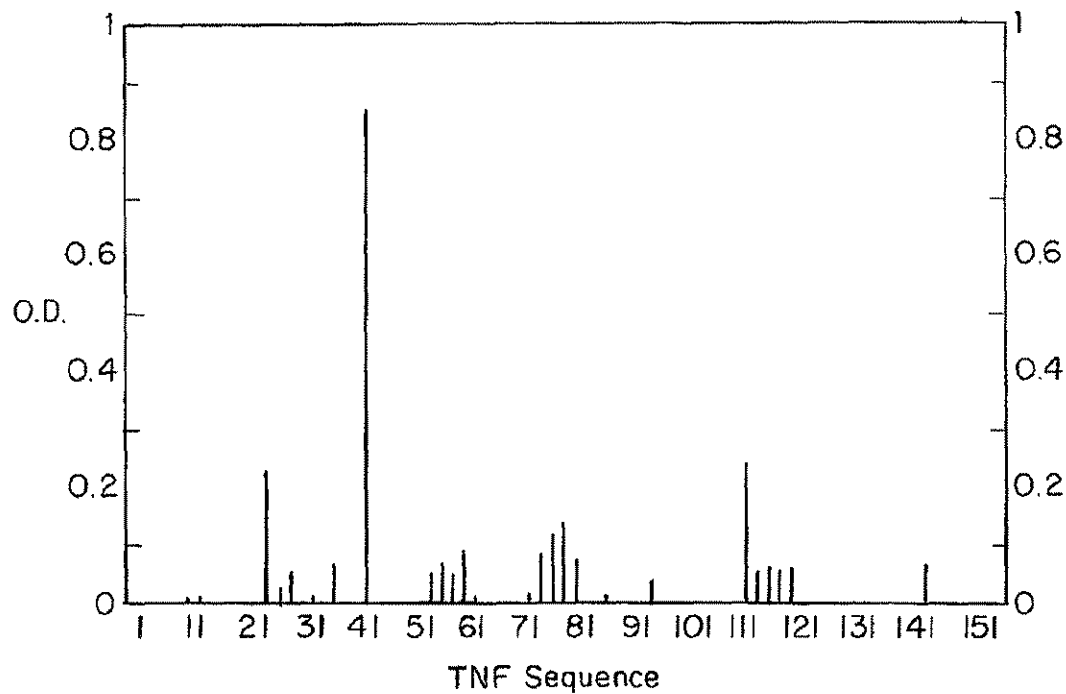


FIG. 14B

U.S. Patent

Jul. 4, 2006

Sheet 14 of 37

US 7,070,775 B2

1	Val Arg Ser Ser Arg Thr Pro Ser Asp	10	Lys Pro Val Ala His Val Val Ala Asn Pro
21	Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala Asn Gly	30	
41	Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser	50	
61	Gln Val Leu Phe Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile	70	
81	Ser Arg Ile Ala Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro	90	
101	Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile Tyr Leu	110	
121	Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp	130	
141	Tyr Leu Asp Phe Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu	150	

FIG. 15

U.S. Patent

Jul. 4, 2006

Sheet 15 of 37

US 7,070,775 B2

GACATCTTGCTGACTCAGTCTCCAGCCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGT
AspIleLeuLeuThrGlnSerProAlaIleLeuSerValSerProGlyGluArgValSer
TTCTCCTGCAGGGCCAGTCAGTTCGTTGGCTCAAGCATCCACTGGTATCAGCAAGAACA
PheSerCysArgAlaSerGlnPheValGlySerSerIleHisTrpTyrGlnGlnArgThr
AATGGTTCTCCAAGGCTTCTCATAAAGTATGCTTCTGAGTCTATGTCTGGATCCCTTCC
AsnGlySerProArgLeuLeuIleLysTyrAlaSerGluSerMetSerGlyIleProSer
AGGTTTAGTGGCAGTGGATCAGGGACAGATTTTACTCTTAGCATCAACACTGTGGAGTCT
ArgPheSerGlySerGlySerGlyThrAspPheThrLeuSerIleAsnThrValGluSer
GAAGATATTGCAGATTATTACTGTCAAGAAAGTCATAGCTGGCCATTACAGTTCGGCTCG
GluAspIleAlaAspTyrTyrCysGlnGlnSerHisSerTrpProPheThrPheGlySer
GGGACAAATTGGAAGTAAAA
GlyThrAsnLeuGluValLys

FIG. 16A

U.S. Patent

Jul. 4, 2006

Sheet 16 of 37

US 7,070,775 B2

GAAGTGAAGCTTGAGGAGTCTGGAGGAGGCTTGGTGCAACCTGGAGGATCCATGAAACTC
 GluValLysLeuGluGluSerGlyGlyGlyLeuValGlnProGlyGlySerMetLysLeu

 TCCTGTGTTGCCCTCTGGATTTCATTTTCAGTAACCACTGGATGAACTGGGTCCGCCAGTCT
 SerCysValAlaSerGlyPheIlePheSerAsnHisTrpMetAsnTrpValArgGlnSer

 CCAGAGAAAGGGCTTGAGTGGGTGCTGAAATTAGATCAAAATCTATTAAATTCTGCAACA
 ProGluLysGlyLeuGluTrpValAlaGluIleArgSerLysSerIleAsnSerAlaThr

 CATTATGCCGAGTCTGTGAAAGGAGGTTTCAACCATCTCAAGAGATGATTCCAAAAGTGCT
 HisTyrAlaGluSerValLysGlyArgPheThrIleSerArgAspSerLysSerAla

 GTGTACCTGCAAATGACCGACTTAAGAACTGAAGACACTGGCGTTTATTACTGTTCAGG
 ValTyrLeuGlnMetThrAspLeuArgThrGluAspThrGlyValTyrTyrCysSerArg

 AATTACTACGGTAGTACCTACGACTACTGGGGCCCAAGGCACCACTCTCACAGTGTCC
 AsnTyrTyrGlySerThrTyrAspTyrTrpGlyGlnGlyThrThrLeuThrValSer

FIG. 16B

U.S. Patent

Jul. 4, 2006

Sheet 17 of 37

US 7,070,775 B2

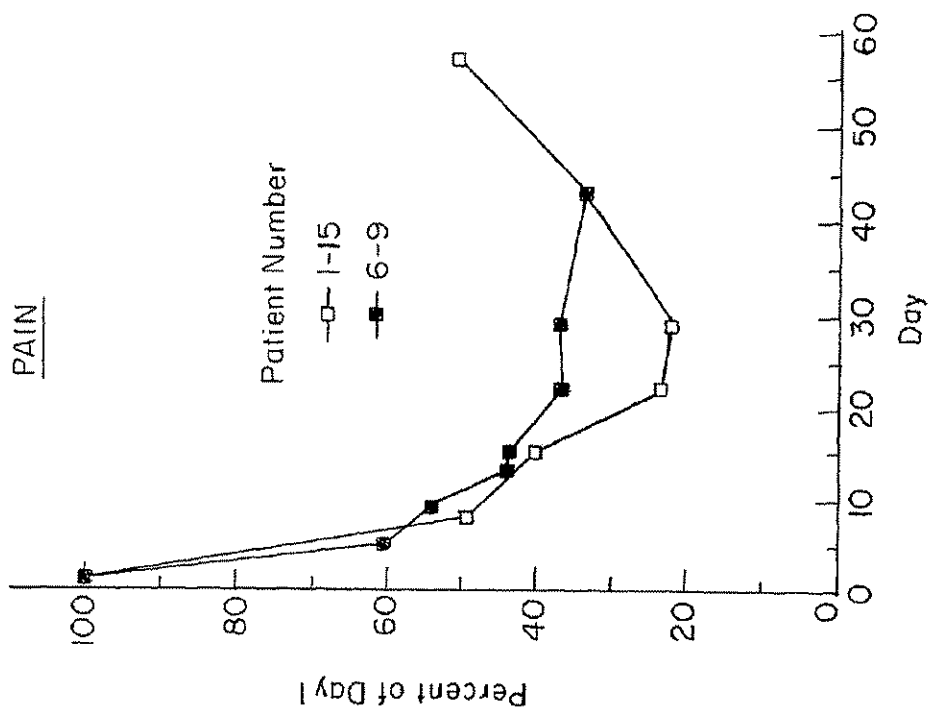


FIG. 18

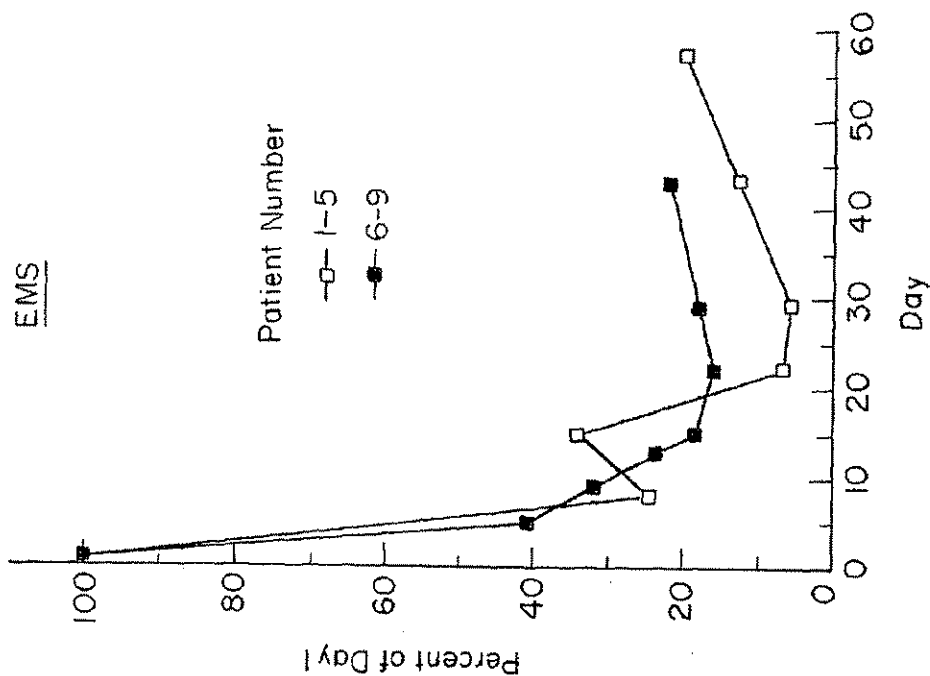


FIG. 17

U.S. Patent

Jul. 4, 2006

Sheet 18 of 37

US 7,070,775 B2

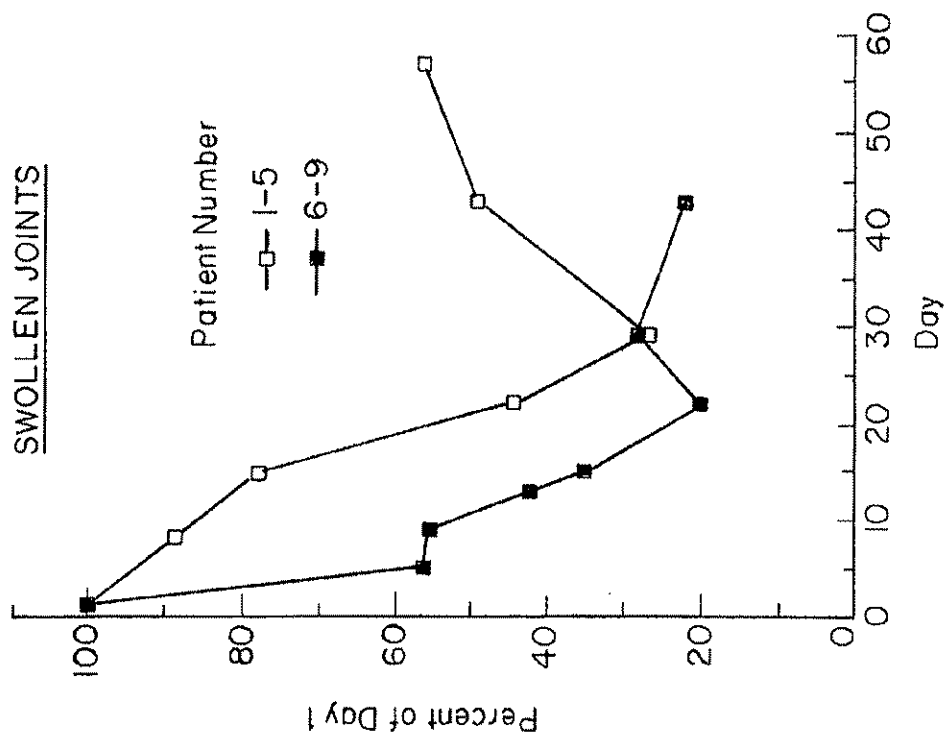


FIG. 20

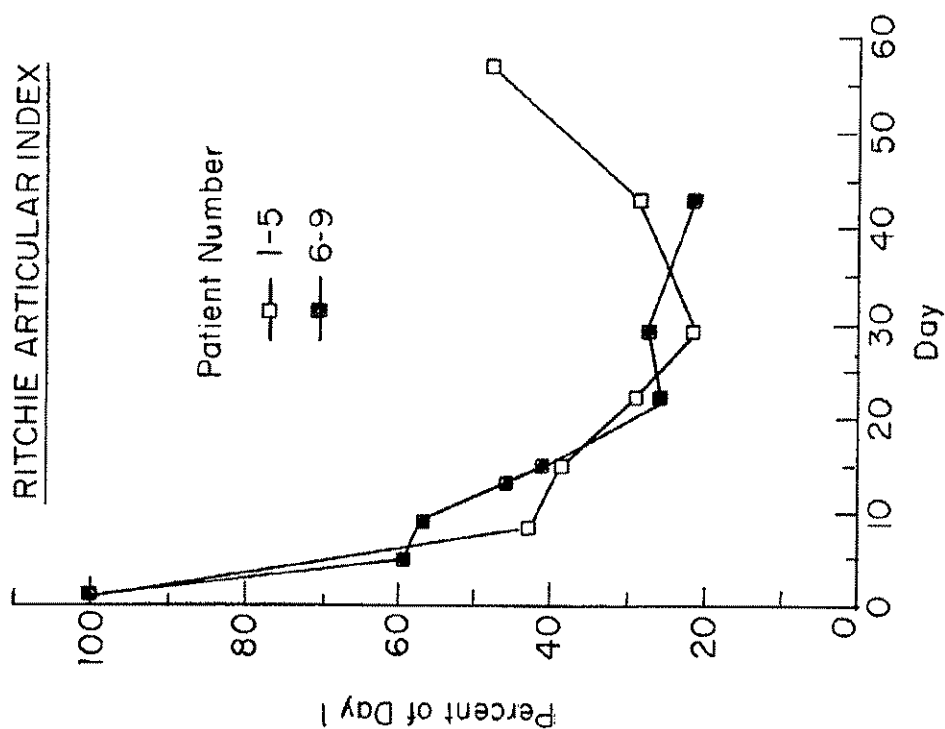


FIG. 19

U.S. Patent

Jul. 4, 2006

Sheet 19 of 37

US 7,070,775 B2

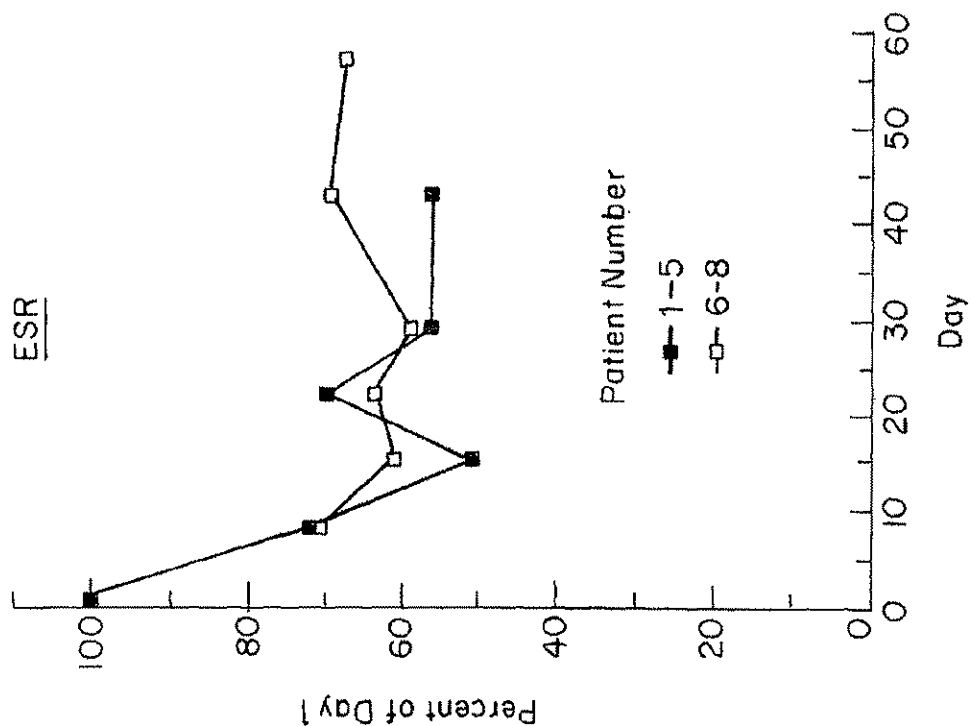


FIG. 22

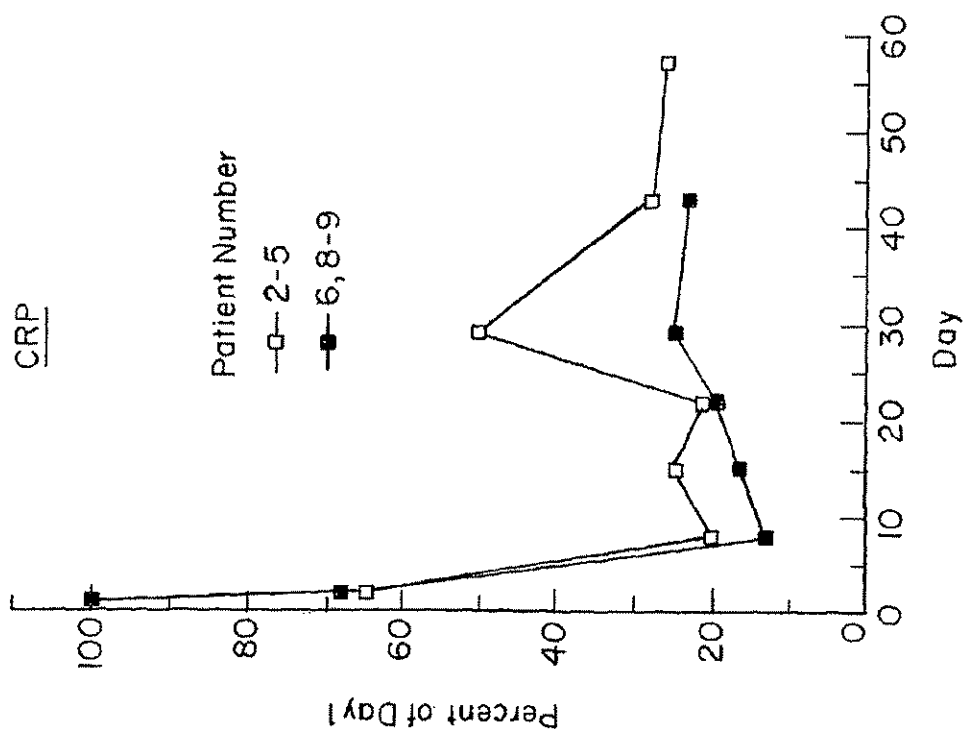


FIG. 21

U.S. Patent

Jul. 4, 2006

Sheet 20 of 37

US 7,070,775 B2

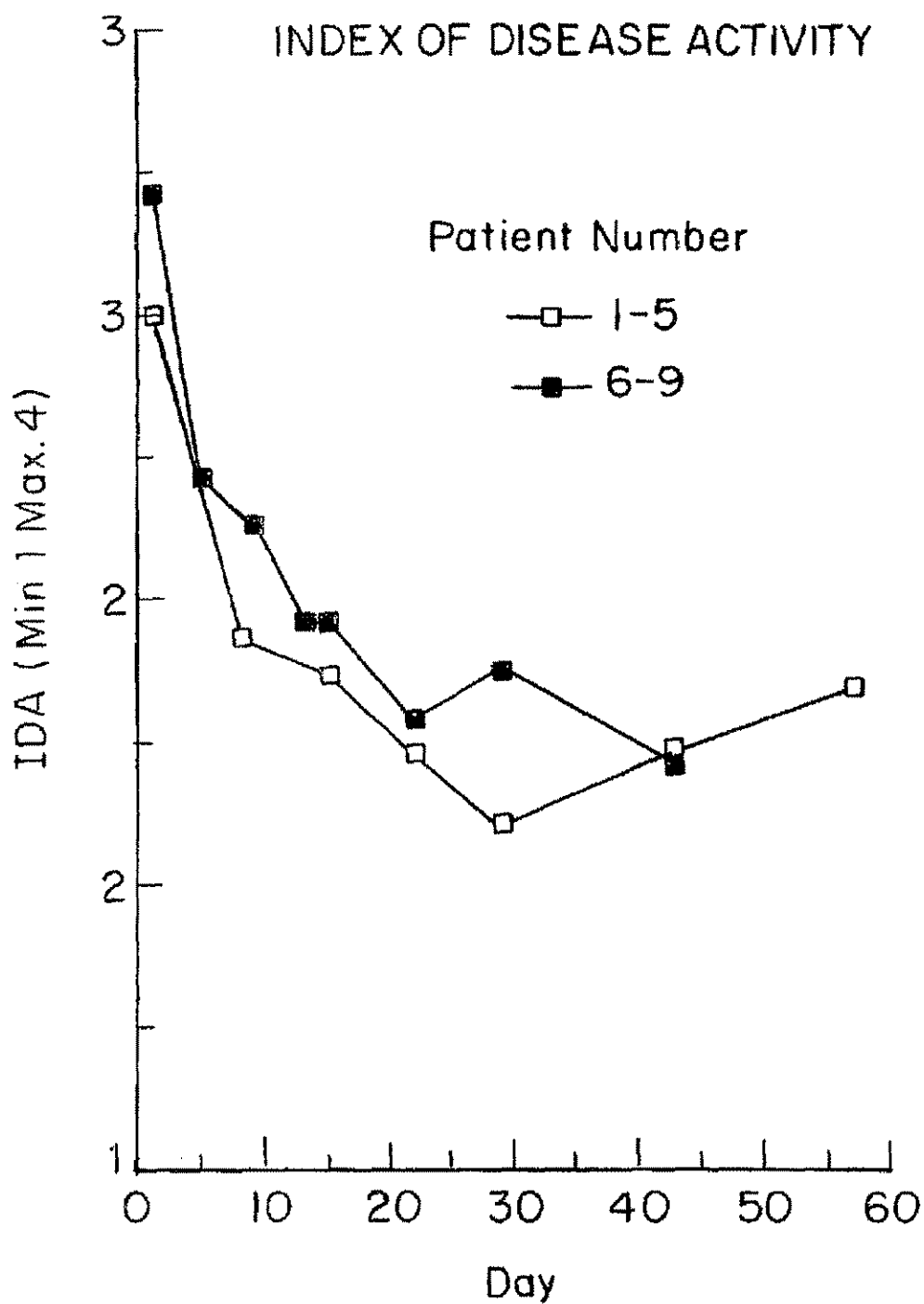


FIG. 23

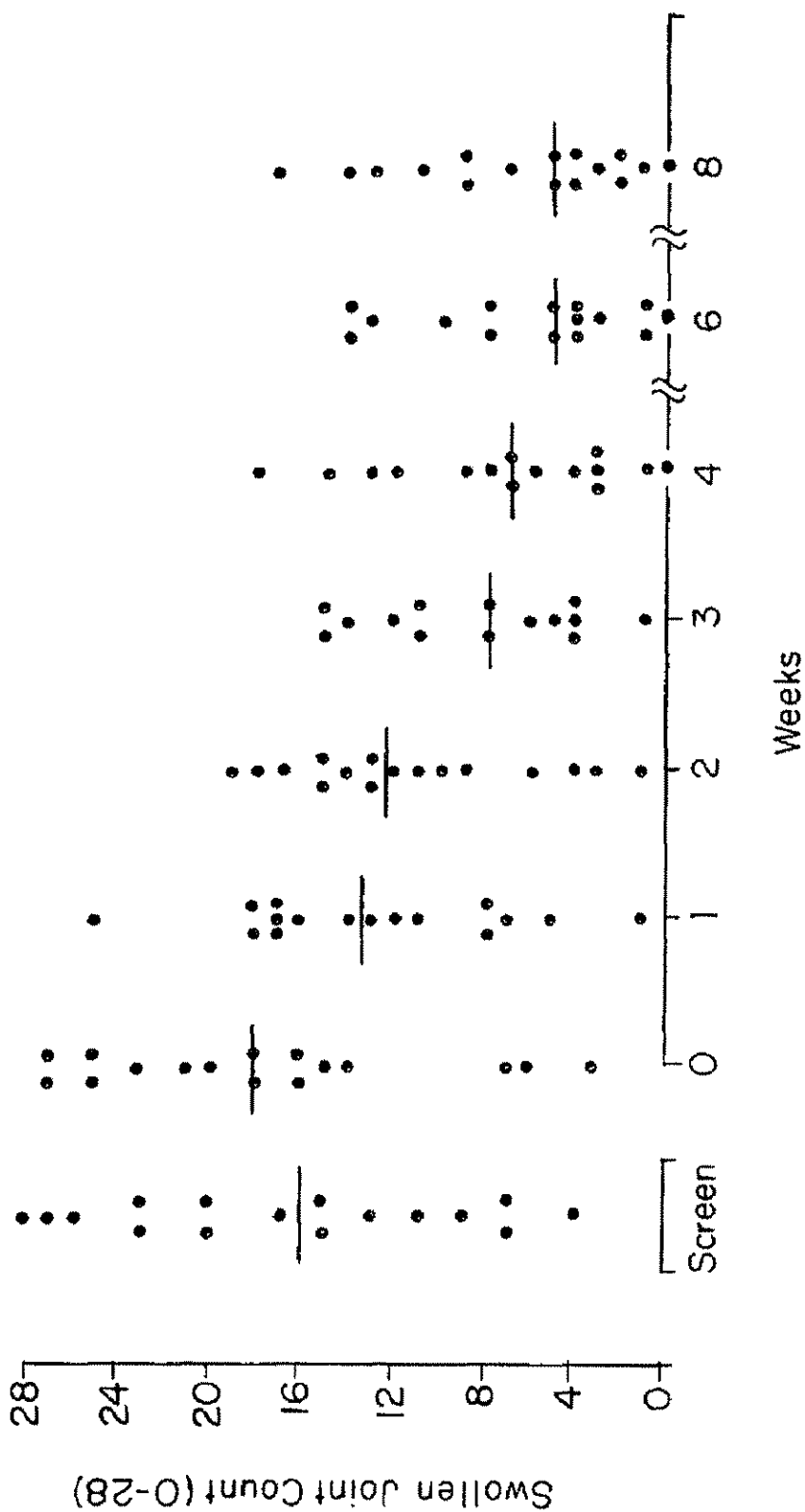


FIG. 24

U.S. Patent

Jul. 4, 2006

Sheet 22 of 37

US 7,070,775 B2

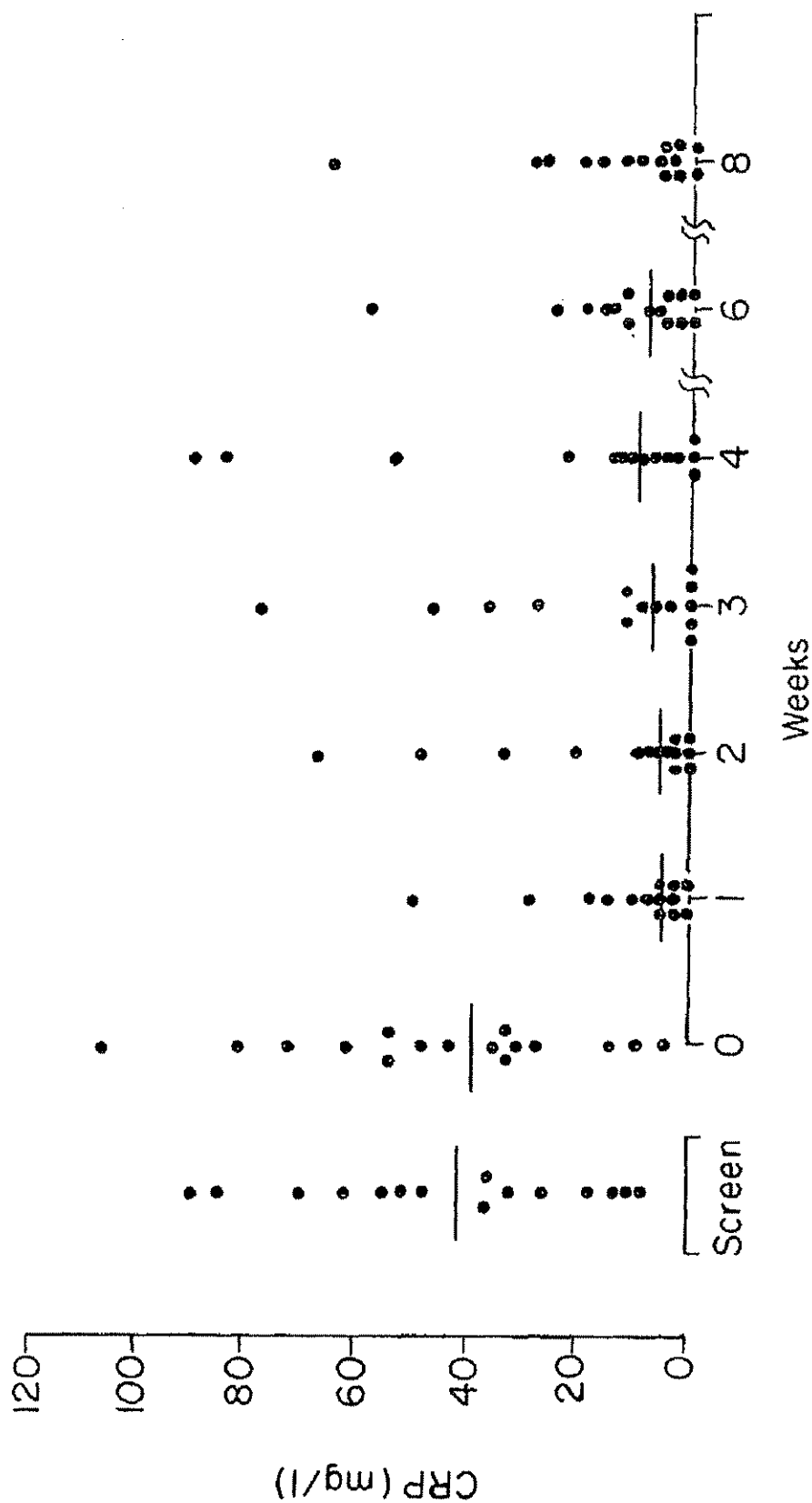


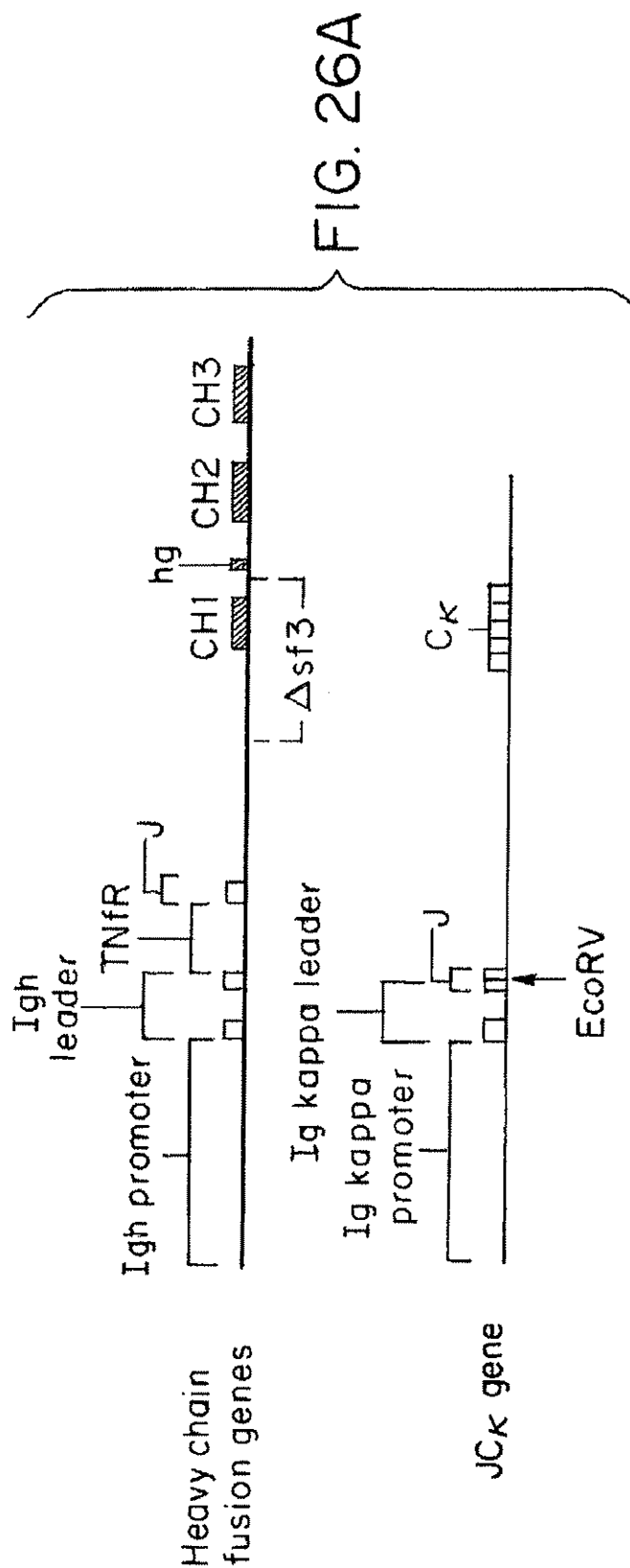
FIG. 25

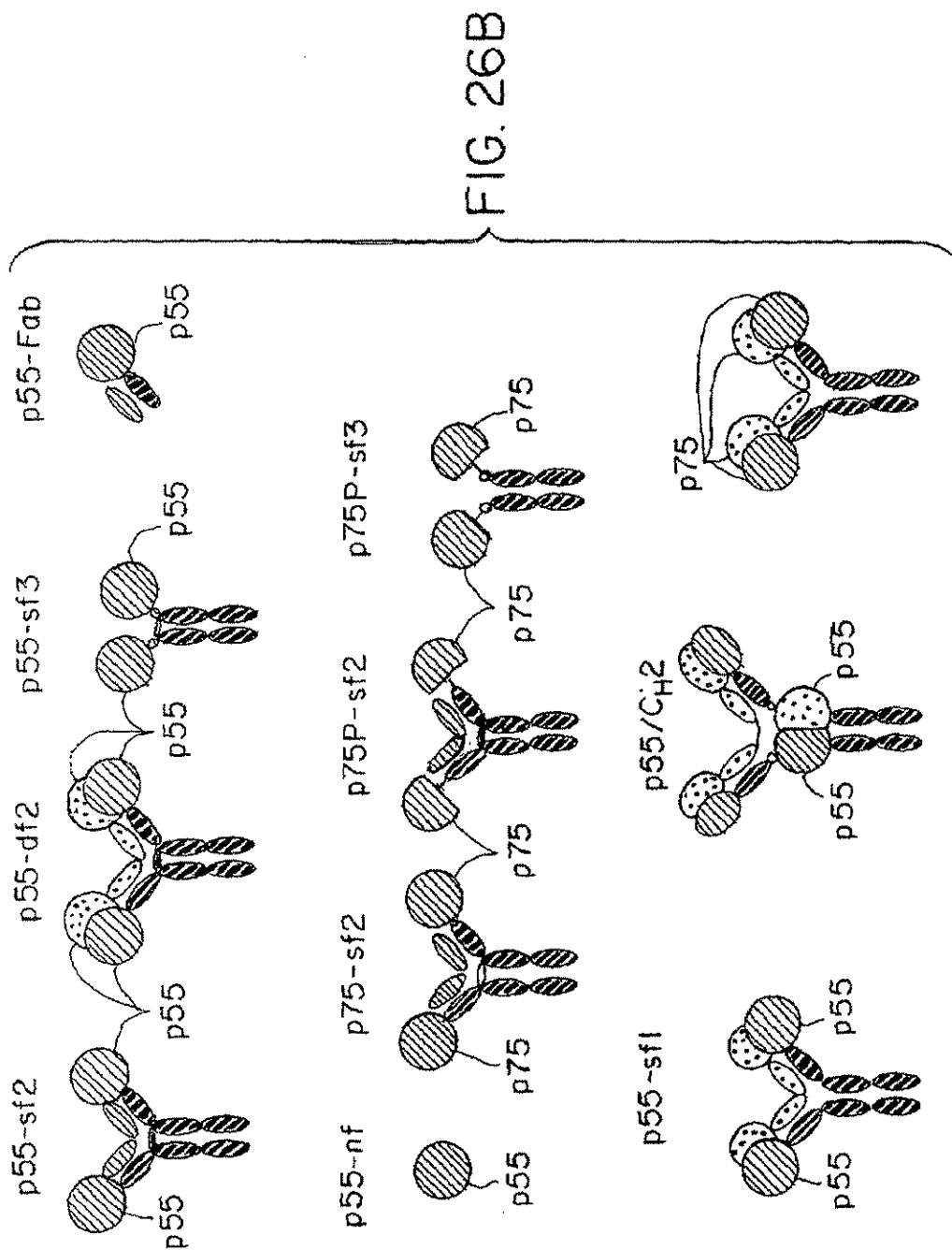
U.S. Patent

Jul. 4, 2006

Sheet 23 of 37

US 7,070,775 B2





[illegible]

U.S. Patent

Jul. 4, 2006

Sheet 26 of 37

US 7,070,775 B2

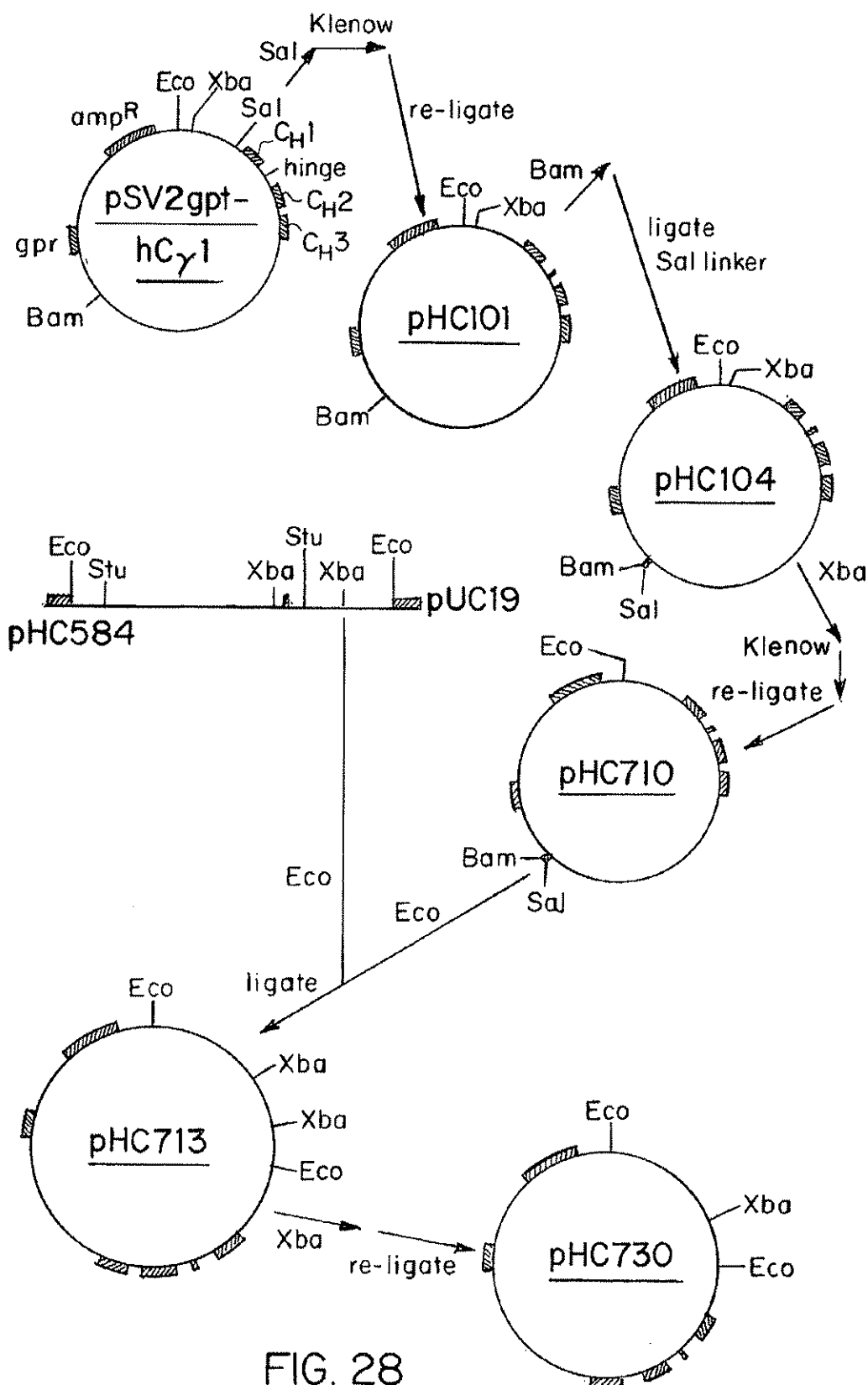


FIG. 28

U.S. Patent

Jul. 4, 2006

Sheet 27 of 37

US 7,070,775 B2

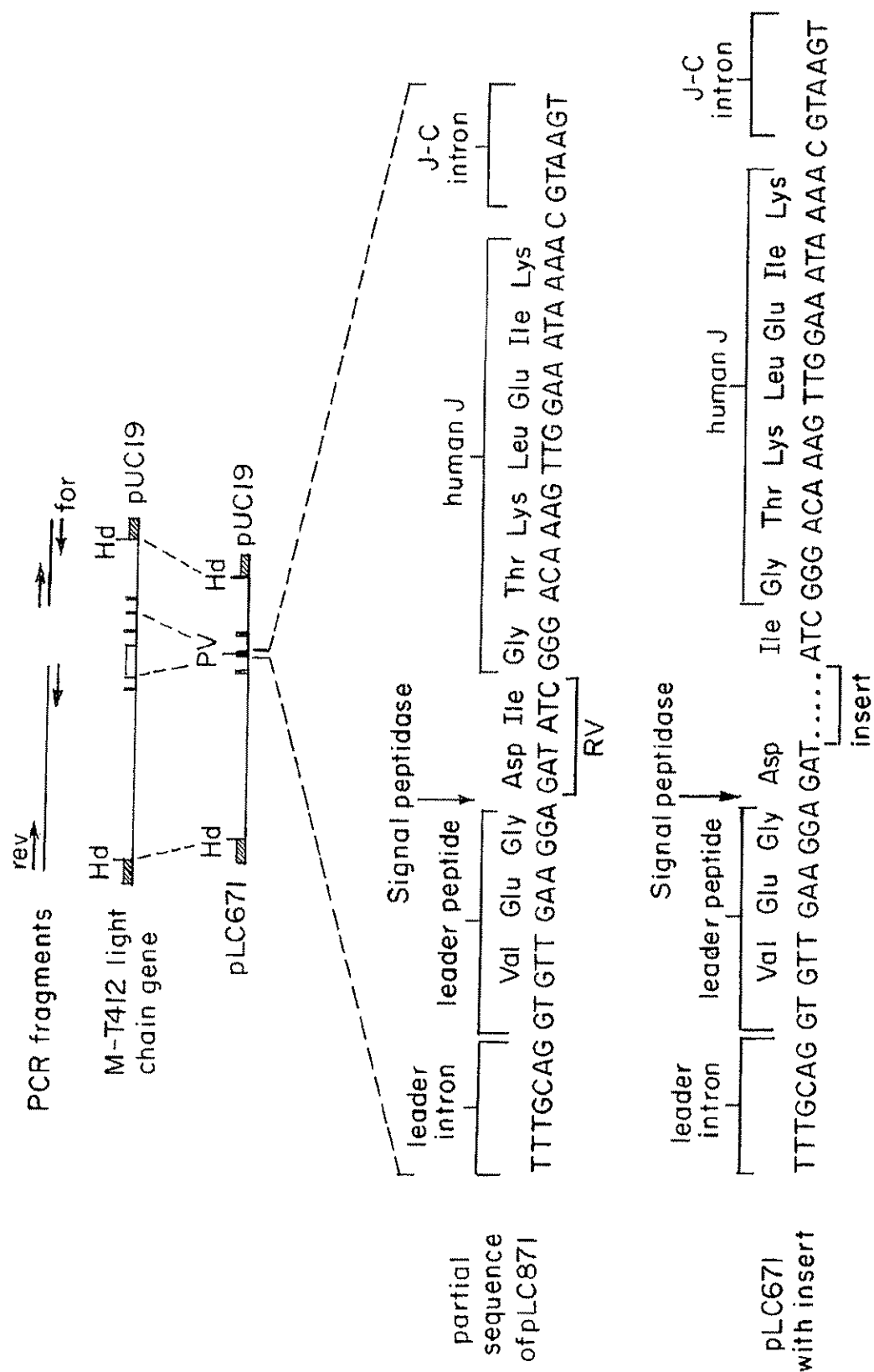


FIG. 29

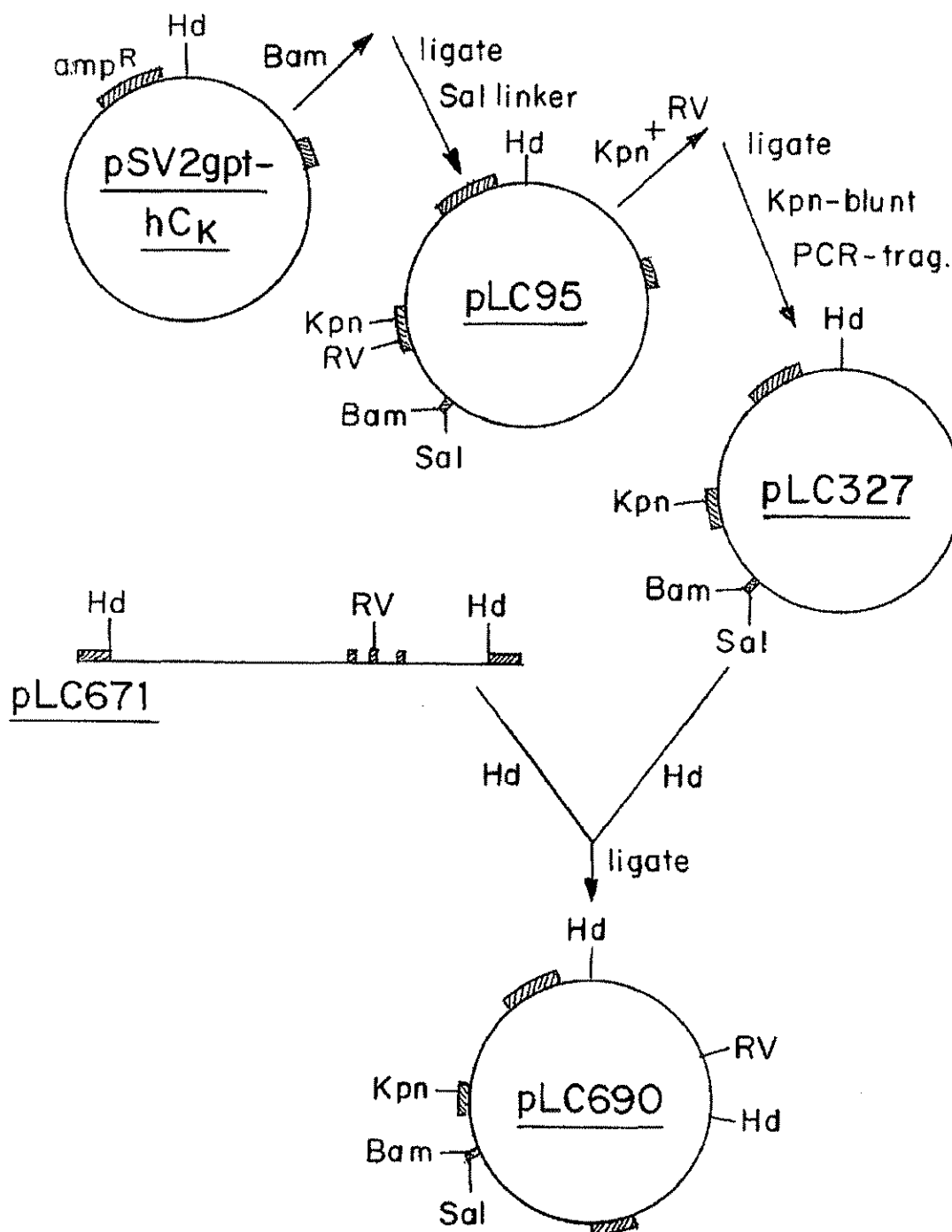


FIG. 30

U.S. Patent

Jul. 4, 2006

Sheet 29 of 37

US 7,070,775 B2

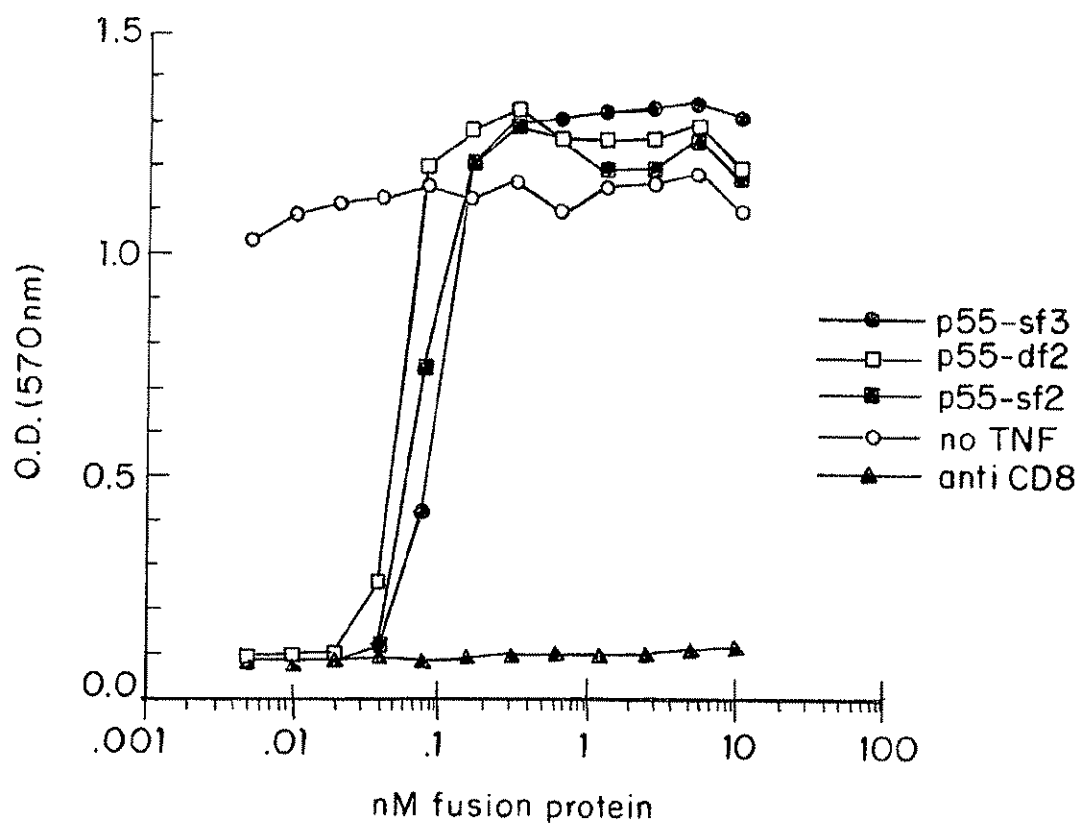


FIG. 31A